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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#4 1/2

IN RE APPLICATION OF

AMLOT ET AL.

APPLICATION NO: 09/770,002

FILED: JANUARY 25, 2001

FOR: USE OF CD25 BINDING MOLECULES IN THE TREATMENT OF RHEUMATOID ARTHRITIS OR SKIN DISEASES

Assistant Commissioner for Patents
Washington, DC 20231

CLAIM OF PRIORITY UNDER 35 USC §119

Sir:

Applicants in the above-identified application hereby claim priority under the International Convention of Application No. GB 9816281.1, filed on July 27, 1998, and Application No. GB 9912460.4, filed on May 27, 1999. These applications are acknowledged in the Declaration of the instant case.

The certified copies of said applications are submitted herewith.

Respectfully submitted,

Susan Hess

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Date: 5/30/01

4-30967/P7

The Patent Office

(3)

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Signed R. Mahoney

Dated 22 June 1999.

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The Patent Office
Cardiff Road
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1.	Your reference	4-30967/P1
2.	Patent application number *(The Patent Office will fill in this part)*	**9912460.4**
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG SCHWARZWALDALLEE 215 4058 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	7125487002
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Organic compounds
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH
	Patents ADP number *(if you know it)*	1800001

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	9
Claim(s)	1
Abstract	
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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	One
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B.A. Yorke & Co.

Date: 27.05.99

B.A. Yorke & Co.

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham
0181 560 5847

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Notes

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Organic Compounds

The invention is directed to the use of a CD25 binding molecule in the treatment of inflammatory and hyperproliferative skin diseases.

More specifically the present invention provides in a first aspect the use of a CD25 binding molecule which comprises at least one antigen binding site comprising at least one domain which comprises in sequence, the hypervariable regions CDR1, CDR2 and CDR3; said CDR1 having the amino acid sequence Arg-Tyr-Trp-Met-His, said CDR2 having the amino acid sequence Ala-Ile-Tyr-Pro-Gly-Asn-Ser-Asp-Thr-Ser-Tyr-Asn-Gln-Lys-Phe-Glu-Gly, and said CDR3 having the amino acid sequence Asp-Tyr-Gly-Tyr-Tyr-Phe-Asp-Phe; or direct equivalents thereof for the treatment of inflammatory and hyperproliferative skin diseases.

Treatment of inflammatory and hyperproliferative skin disease includes control or amelioration of the disease and/or its sequellae, e.g. symptoms, as well as control or amelioration of aetiological components. Treatment of e.g. psoriasis also includes suppression of further clinical relapse.

Inflammatory and hyperproliferative skin diseases include psoriasis, atopical dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus and acne.

Preferably a CD25 binding molecule is used comprising at least one antigen binding site comprising:

a) a first domain comprising in sequence the hypervariable regions CDR1, CDR2 and CDR3; said CDR1 having the amino acid sequence Arg-Tyr-Trp-Met-His, said CDR2 having the amino acid sequence Ala-Ile-Tyr-Pro-Gly-Asn-Ser-Asp-Thr-Ser-Tyr-Asn-Gln-Lys-Phe-Glu-Gly, and said CDR3 having the amino acid sequence Asp-Tyr-Gly-Tyr-Tyr-Phe-Asp-Phe and,

b) a second domain comprising in sequence the hypervariable regions CDR1', CDR2' and CDR3', said CDR1' having the amino acid sequence Ser-Ala-Ser-Ser-Ser-Ile-Ser-Tyr-Met-Gln, said CDR2' having the amino acid sequence Asp-Thr-Ser-Lys-Leu-Ala-Ser, and said CDR3' having the amino acid sequence His-Gln-Arg-Ser-Ser-Tyr-Thr;

or direct equivalents thereof.

Unless otherwise indicated, any polypeptide chain is herein described as having an amino acid sequence starting at the N-terminal extremity and ending at the C-terminal extremity.

When the antigen binding site comprises both the first and second domains, these may be located on the same polypeptide molecule or, preferably, each domain may be on a different chain, the first domain being part of an immunoglobulin heavy chain or fragment thereof and the second domain being part of an immunoglobulin light chain or fragment thereof.

Accordingly, the invention also provides the use of a CD25 binding molecule which comprises at least one antigen binding site comprising either a first domain having an amino acid sequence identical or substantially identical to that shown in Seq. Id. No. 1 in EP 449,769, the contents of which is herein incorporated by reference, starting with amino acid at position 1 and ending with amino acid at position 117 or a first domain as described above and a second domain having an amino acid sequence identical or substantially identical to that shown in Seq. Id. No. 2 in EP 449,769, the contents of which is herein incorporated by reference, starting with amino acid at position 1 and ending with amino acid at position 104 for the treatment of inflammatory and hyperproliferative skin diseases.

A more preferred CD25 binding molecule for use for the treatment of inflammatory and hyperproliferative skin diseases is selected from a chimeric anti-CD25 antibody which comprises at least

a) one immunoglobulin heavy chain or fragment thereof which comprises (i) a variable domain comprising in sequence the hypervariable regions CDR1, CDR2 and CDR3 and (ii) the constant part or fragment thereof of a human heavy chain; said CDR1 having the amino acid sequence Arg-Tyr-Trp-Met-His, said CDR2 having the amino acid sequence Ala-Ile-Tyr-Pro-Gly-Asn-Ser-Asp-Thr-Ser-Tyr-Asn-Gln-Lys-Phe-Glu-Gly, and said CDR3 having the amino acid sequence Asp-Tyr-Gly-Tyr-Tyr-Phe-Asp-Phe and

b) one immunoglobulin light chain or fragment thereof which comprises (i) a variable domain comprising in sequence the hypervariable regions CDR1', CDR2' and CDR3' and (ii) the constant part or fragment thereof of a human light chain; said CDR1' having the amino acid sequence Ser-Ala-Ser-Ser-Ser-Ile-Ser-Tyr-Met-Gln, said CDR2' having the amino acid se-

quence Asp-Thr-Ser-Lys-Leu-Ala-Ser, and said CDR3' having the amino acid sequence His-Gln-Arg-Ser-Ser-Tyr-Thr;
and direct equivalents thereof.

Alternatively, a CD25 binding molecule for the treatment of inflammatory and hyperproliferative skin diseases may be selected from a single chain binding molecule which comprises an antigen binding site comprising
a) a first domain comprising in sequence the hypervariable regions CDR1, CDR2 and CDR3, said hypervariable regions having the amino acid sequences as shown in Seq. Id. No. 1 in EP 449,769, the contents of which is herein incorporated by reference,
b) a second domain comprising in sequence the hypervariable regions CDR1', CDR2' and CDR3', said hypervariable regions having the amino acid sequences as shown in Seq. Id. No. 2 in EP 449,769, the contents of which is herein incorporated by reference, and
c) a peptide linker which is bound either to the N-terminal extremity of the first domain and to the C-terminal extremity of the second domain or to the C-terminal extremity of the first domain and to the N-terminal extremity of second domain;
and direct equivalents thereof.

As it is well known, minor changes in an amino acid sequence such as deletion, addition or substitution of one or several amino acids may lead to an allelic form of the original protein which has identical or substantially identical properties. Thus, by the term "direct equivalents thereof" is meant either any single domain CD25 binding molecule (molecule X)
(i) in which the hypervariable regions CDR1, CDR2 and CDR3 taken as a whole are at least 80 % homologous, preferably at least 90 % homologous, more preferably at least 95 % homologous to the hypervariable regions as shown in Seq. Id. No. 1 in EP 449,769, the contents of which is herein incorporated by reference, and,
(ii) which is capable of inhibiting the binding of Interleukin 2 (IL-2) to its receptor substantially to the same extent as a reference molecule having framework regions identical to those of molecule X but having hypervariable regions CDR1, CDR2 and CDR3 identical to those shown in Seq. Id. No. 1 in EP 449,769, the contents of which is herein incorporated by reference;
or any CD25 binding molecule having at least two domains per binding site (molecule X')
(i) in which the hypervariable regions CDR1, CDR2, CDR3, CDR1', CDR2' and CDR3' taken as a whole are at least 80 % homologous, preferably at least 90 % homologous, more pre-

ferably at least 95 % homologous to the hypervariable regions as shown in Seq. Id. No. 1 and 2 in EP 449,769, the contents of which is herein incorporated by reference, and
(ii) which is capable of inhibiting the binding of IL-2 to its receptor substantially to the same extent as a reference molecule having framework regions and constant parts identical to molecule X' but having hypervariable regions CDR1, CDR2, CDR3, CDR1', CDR2' and CDR3' identical to those shown in Seq. Id. No. 1 and 2 in EP 449,769, the contents of which is herein incorporated by reference,.

This last criterion may be conveniently tested in various assays as described in EP 449,769, the contents of which is herein incorporated by reference.

Most preferably, the chimeric CD25 antibody for the treatment of inflammatory and hyperproliferative skin diseases comprises at least
a) one heavy chain which comprises a variable domain having an amino acid sequence identical or substantially identical to that shown in Seq. Id. No. 1 in EP 449,769, the contents of which is herein incorporated by reference, starting with amino acid at position 1 and ending with amino acid at position 117 and the constant part of a human heavy chain; and
b) one light chain which comprises a variable domain having an amino acid sequence identical or substantially identical to that shown in Seq. Id. No. 2 in EP 449,769, the contents of which is herein incorporated by reference, starting with glutamic acid at position 1 and ending with glutamic acid at position 104 and the constant part of a human light chain.

The constant part of a human heavy chain may be of the $\gamma 1$, $\gamma 2$, $\gamma 3$, $\gamma 4$, μ, $\alpha 1$, $\alpha 2$, δ or ε type, preferably of the γ type, more preferably of the $\gamma 1$ type, whereas the constant part of a human light chain may be of the κ or λ type (which includes the $\lambda 1$, $\lambda 2$ and $\lambda 3$ subtypes) but is preferably of the κ type. The amino acid sequence of all these constant parts are given in Kabat et al., Sequences of Proteins of Immunological Interest, US Department of Health and Human Services, Public Health Service, NIH..

The most preferred CD25 binding molecule is basiliximab which is commercially available as SIMULECT® from Novartis AG.
A CD25 binding molecule for the treatment of inflammatory and hyperproliferative skin diseases may be produced by techniques disclosed for example in EP 449,769, the contents of which is herein incorporated by reference, in particular in Examples 1 to 5 of EP 449,769.

Therefore the invention also provides

(i) a method of treatment of inflammatory and hyperproliferative skin diseases in a patient in need of such treatment comprising administering to the patient an effective amount of a CD25 binding molecule as described above.

(ii) a pharmaceutical composition for treatment of inflammatory and hyperproliferative skin diseases which comprises a CD25 binding molecule as described above and a pharmaceutically acceptable carrier or diluent.

(iii) a CD25 binding molecule as described above for use in the manufacturing of a medicament for use in the method as described in (i).

(iv) a method as described in (i) comprising co-administration, e.g. concomitantly or in sequence, of an effective amount of a CD25 binding molecule as described above and a further drug substance being effective in the treatment of inflammatory and hyperproliferative skin diseases.

(v) a method as described in (i) comprising administration of an effective amount of a CD25 binding molecule as described above and application of a non-drug inflammatory and hyperproliferative skin disease therapy, e.g. UV light therapy.

(vi) a method as described in (iv) combined with the method as described in (v).

For the use in accordance with the invention, the appropriate dosage will, of course, vary depending upon, for example, the particular molecule to be employed, the host, the mode of administration and the severity of the condition being treated and the effects obtained. Satisfactory results are generally indicated to be obtained at dosages from about 0.1 mg to about 100 mg. Administration may be in a single dose or in several doses over a period of time as long as may be indicated in relation to the time the inflammatory and hyperproliferative skin disease is clinically evident or prophylactically to suppress further clinical relapse, for example a dose of 10 to 100 mg may be administered with a time-lag of one week to five weeks, e.g. every four weeks, up to a time control or amelioration of the disease is achieved. The CD25 binding molecule is conveniently administered parenterally, normally intravenously, for example, into the antecubital or other peripheral vein. An exemplary dosing regimen is intravenous administration of 40 mg every 28 days until control or amelioration of the disease is achieved.

Pharmaceutical compositions of the invention may be manufactured in a conventional manner as described, e.g. in EP 449,769, the contents of which is herein incorporated by reference.

The monoclonal antibodies specific for IL-2R may be administered as the sole active ingredient or together with other drugs in immunomodulating regimens or other anti-inflammatory agents. For example, the monoclonal antibodies specific for IL-2R may be used in combination with cyclosporins, rapamycins or ascomycins, or their immunosuppressive analogs, e.g. cyclosporin A, cyclosporin G, FK-506, rapamycin etc.; corticosteroids; cyclophosphamide; azathioprene; methotrexate; brequinar; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine; other immuno-suppressive monoclonal antibodies, e.g. monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, CD7, CD28, B7, CD40, CD45, or CD58 or their ligands; or other immunomodulatory compounds, e.g. CTLA4Ig.

The intravenous infusions may be prepared as follows: the lyophylized antibodies are mixed together and dispersed into 100 ml sterile buffered saline containing 4.5% wt. of human albumin. This saline dispersion may be administered to the patients either as an intravenous bolus injection or as an intravenous infusion over a 15 minute period.

Investigations so far indicate that the administration of the CD25 binding molecules is free from unacceptable side-effects at the dosage levels employed. Particularly the preferred one, basiliximab, is safe, approved by the Federal Drug Administration (FDA) of the United States and is commercially available.

Utility of the CD25 binding molecule for the treatment of inflammatory and hyperproliferative skin diseases, e.g. psoriasis, is shown in the following clinical example.

24 patients (both male and female) between the ages of 18-70 years of age with moderate to severe plaque psoriasis defined as having a regional or total PASI $\geq$ 10 *and* affected BSA $\geq$ 5% enter into the Screening period (Visit 1, Week -2) and are randomized into one of two basiliximab dose groups (40 mg or 60 mg).
There is no concomitant systemic anti-psoriatic therapy at anytime during the study and no use of any specific topical anti-psoriatic therapies at any time after successful screening to

the end of the study. All concomitant medication taken at the start of the study and during the course of the study are recorded.

Basiliximab is reconstituted immediately prior to administration as recommended, i.e. Vehicle (5 ml) is injected into the vial and the lyophilisate redissolved with gentle swirling or inversion. The vials are not shaken, and frothing is avoided. For each randomized patient's dose, basiliximab vials contain either: 20 mg vial X 2 and 1 placebo vial; or 20 mg vial X 3. After the first basiliximab 40 mg or 60 mg (depending on initial randomization) dose is administered, all subsequent basiliximab 40 mg or 60 mg 15 min iv infusion doses are administered within 48 h of receipt of every blood flow cytometry measurement demonstrating unsaturated peripheral blood lymphocyte IL-2 receptors during a 12 week treatment period. Blood draws for blood flow cytometry measurement occur every 2-weeks at each scheduled patient visit to measure the percent peripheral blood lymphocyte IL-2 receptor saturation. Saturation is defined and reported as a ≥ 95% reduction in CD25 cells with complete IL-2 receptor saturation and unsaturation is defined and reported as ≤ 95% CD25 cells with complete IL-2 receptor saturation.

Each patient is evaluated every 2 weeks for efficacy (PASI, % affected BSA, global and overall psoriasis evaluation) and photographed using standard photographic methods. Additionally, four serial lesional skin biopsies are taken of all patients enrolled for histologic evaluation using both immune markers and standard staining methods.

Efficacy assessments: Baseline efficacy measurements performed/obtained at the screening visit and at each scheduled visit during the 12-week treatment and 8-week follow-up periods include PASI, % affected BSA, and global psoriasis evaluation.

Primary efficacy variable: Change from baseline in the PASI.

Secondary efficacy variables: Change from baseline in % affected BSA (Rule of 9's).

Time (in days) to clinical remission (defined as 75% reduction of baseline PASI score), if obtained.

Length (in days) of clinical remission.

Change from baseline in the global psoriasis evaluation.

Investigator's overall psoriasis evaluation.

Patient's overall psoriasis evaluation.

Calculation of the PASI: The head (0.1), trunk (0.3), upper limbs (0.2) and lower limbs (0.4) are assessed separately for erythema, infiltration, scaling. The average degree of severity of each symptom in each of the four body parts, is assigned a score of 0-4. The area covered by lesions on each body part is estimated as a percentage of the total area of that particular body

part and score from 0-6 is then assigned. This evaluation takes into account the true area affected and not a 'functional' area affected. Further practical details help the assessment:

1) The buttocks count as part of the legs.
2) The axillae and groin count as part of the trunk.
3) The neck counts as part of the head.
4) When scoring the severity of erythema, scales are not removed.

PASI - Scoring System					
Score	0	1	2	3	4
Erythema Infiltration Desquamation	none	slight	moderate	severe	very severe

PASI - Scoring System							
Score	0	1	2	3	4	5	6
True Area %	0%	1%-9%	10%-29%	30%-49%	50%-69%	70%-89%	90%-100%

The total score for each body part is obtained by multiplying the sum of the severity scores of the 3 basic lesions by the area score, then multiplying the result by the constant weighted value (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4) assigned to that body part. The sum of the scores of the individual body parts gives the PASI.

Affected surface determination (rule of 9's): An estimate of the percent BSA affected with psoriasis is estimated. Each section of the body is labeled with the percent of the total BSA it represents.

Overall psoriasis evaluation: An overall evaluation by patient and investigator is performed comparing impression of improvement while on the drug when related to pretreatment condition. The following scale is used: 1 = very good; 2 = good; 3 = moderate; 4 = slight; 5 = none.

The investigator's and patient's overall psoriasis evaluation are performed at Visit 6 (Week 6), Visit 7 (Week 8), Visit 8 (Week 10), Visit 9 (Week 12), Visit 10 (Week 16), and Visit 11 (Week 20).

Global psoriasis evaluation: A global evaluation of the current status of the disease is rated by the investigator using the following scale: 1 = totally clear; 2 = almost clear; 3 = mild; 4 = mild-moderate; 5 = moderate; 6 = moderate-severe; 7 = severe.

Biopsies: 4 mm punch biopsies of lesional psoriatic skin are performed using standard clinical practice and sterile technique. Biopsy samples are placed faced down in the supplied cryomold and filled with OCT compound. The cryomold is stored at -70°C in a dry-ice-alcohol slurry.

Epidermal thickness, K-16 and ICAM-1 expression, and epidermal CD3/CD25 and dermal CD25 cell count, as well as percent CD25 cells with IL-2 receptor saturation are evaluated using standard histology methods. A baseline biopsy is performed prior to basiliximab injection. The second occurs at Visit 4. If blood flow cytometry at Visit 4 demonstrates full receptor saturation, then the 3rd biopsy occurs at the next visit (scheduled visit or unscheduled visit as necessary) that the blood flow cytometry demonstrates *unsaturated receptors.* However, if the blood flow cytometry at Visit 4 shows unsaturated receptors, then the 3rd biopsy is performed at the next visit (scheduled visit or unscheduled visit as necessary) that the blood flow cytometry shows *saturated receptors.* The fourth biopsy is performed at Visit 10 (week 16). All biopsies are performed in the same plaque. If the plaque no longer is present as treatment has caused resolution, then a biopsy is still performed in the area where the plaque was previously present.

Patients receiving basiliximab show a marked improvement with respect to PASI, Global Psoriasis Evaluation, BSA, and Overall Psoriasis Evaluation as compared to patients receiving placebo.

Claims

1. The use of a CD25 binding molecule which comprises at least one antigen binding site comprising at least one domain which comprises in sequence, the hypervariable regions CDR1, CDR2 and CDR3; said CDR1 having the amino acid sequence Arg-Tyr-Trp-Met-His, said CDR2 having the amino acid sequence Ala-Ile-Tyr-Pro-Gly-Asn-Ser-Asp-Thr-Ser-Tyr-Asn-Gln-Lys-Phe-Glu-Gly, and said CDR3 having the amino acid sequence Asp-Tyr-Gly-Tyr-Tyr-Phe-Asp-Phe; or direct equivalents thereof for the treatment of inflammatory and hyperproliferative skin diseases.

2. A method of treatment of inflammatory and hyperproliferative skin diseases in a patient in need of such treatment comprising administering to the patient an effective amount of a CD25 binding molecule according to claim 1.

3. A CD25 binding molecule e.g. substantially as hereinbefore defined and described for use in the manufacturing of a medicament for use in the method according to claim 2.

4. A pharmaceutical composition comprising a CD25 binding molecule e.g. substantially as hereinbefore defined and a pharmaceutically acceptable carrier or diluent for use in the method according to claim 2 or in the manufacturing according to claim 3.

5. A method according to claim 2 comprising co-administration, e.g. concomitantly or in sequence, of an effective amount of a CD25 binding molecule, e.g. substantially as hereinbefore defined and described and a further drug substance being effective for the treatment of inflammatory and hyperproliferative skin diseases.

6. A method according to claim 2 comprising administration of an effective amount of a CD25 binding molecule, e.g. substantially as hereinbefore defined and described, and application of a non-drug inflammatory and hyperproliferative skin diseases therapy.

7. The method according to claim 5 combined with the method of claim 6.